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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/393,066	02/23/1995	JOHN H. WOLFE	PENN-0065	1030

7590 04/06/2005

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 04/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 08/393,066
Filing Date: February 23, 1995
Appellant(s): WOLFE ET AL.

Jane Massey Licata
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed January 20, 2005.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences, which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

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(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 1 and 3-9 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7). Appellant's statement is in agreement that claims 1 and 3-9 stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct. For the above reasons, it is believed that the rejections should be sustained.

(9) Prior Art of Record

Blau et al. Molecular Medicine: Gene Therapy - A Novel From of Drug Delivery. The New England Journal of Medicine. November 2, 1995, pages 1204-1207.

Verma et al. Gene Therapy - Promises, Problems and Prospects. Nature, Vol. 389, 18 September 1997, pages 239-242

Gene Therapy's Growing Pains. Science. Vol. 269, 25 August 1995, pages 1050-1055.

Anderson. Gene Therapy. Scientific American. September 1995, pages 124-126 and 128.

Fink et al. Advances in the Development of Herpes Simplex Virus-Based Gene Transfer Vectors of the Nervous System. Clinical Neuroscience. Volume 3, 1996, pages 284-291.

Blomer et al. Applications of Gene Blomer et al. Applications of Gene Therapy to the CNS. Human Molecular Genetics. Vol. 5 Review, 1996, pages 1397-1404.

Eck et al. Gene Based Therapy in The Pharmacological Basis of Therapeutics, Goodman and Gillman, eds. 9th edition, McGraw- Hill, New York, 1996, 77-101.

Wolfe et al. Herpesvirus Vector Gene Transfer and Expression of B-Glucuronidase in the Central Nervous System of MPS VII Mice. Nature Genetics. Vol. 1, August 1992, pages 379-384.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 3-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record set forth in all previous office actions. The entire rejection is reiterated below.

Nature of the Invention

Claims 1 and 3-9 are drawn to a method of stably expressing a selected DNA sequence in the central nervous system of a mammal, comprising administering to the mammal a neurotropic virus which infects cells of central nervous system of the mammal, the vector containing a selected DNA sequence operatively linked to a selected promoter so

selected DNA sequence is stably expressed by infected central nervous system cells, to a method of stably expressing β-glucuronidase in the brain of a mammal comprising administering to the mammal a neurotropic viral vector which infects cells of the brain of the mammal, said vector being and HSV-1 vector containing a DNA sequence encoding β-glucuronidase operatively linked to a LAT promoter, so that the infected brain cells stably express β-glucuronidase.

While the claimed invention requires only stable expression of the selected DNA sequence, the specification provides no use for mere stable expression. The specification is very clear that the purpose of the delivery method to produce a gene therapy (specification, page 2, line 3 to page 3, line 17; page 8, lines 9-13; page 9, line 34 to page 10, line 9; page 16, lines 1-17 and page 20, lines 7-10). At each of these citations, the specification discloses that the method can be used to deliver genes to the CNS to treat a variety of diseases such as Parkinson's Disease and Lesch-Nyhan Disease. The specification does not disclose a use for the claimed method of delivery absent a treatment or therapeutic effect. As the artisan reads the specification to gain guidance on using of an invention, the artisan would see only that the claimed method has a use as a gene therapy. The art does not provide guidance to other uses for in vivo gene delivery absent a therapy. Thus, the claims are not enabled when read in view of the specification. However, applicant should point to page and line number where non-therapeutic uses are disclosed.

State of the Art at the Time of Filing

At the time of filing, gene therapy was not developed sufficiently that the mere showing of delivery of a gene to a particular tissue would have been viewed as enabling gene therapy. To achieve a therapeutic effect, an amount of a neurotropic viral vector would need to be delivered to the appropriate tissue and expressed sufficiently to provide an alleviation of some symptoms associated with a particular disease.

The artisan would not have considered the specification as enabling as the specification fails to provide sufficient guidance methods of stably expressing a DNA sequence of interest in the CMS of a mammal such that such expression would result in a therapeutic effect. Several references that summarize the art at the time of filing indicate that vector; vector delivery and extent of expression were critical limitations to gene therapy. Verma states that the Achilles heel of gene therapy is gene delivery, and that the problem lies in the inability to deliver gene efficiently and obtain sustained expression (see Verma, page 239, col. 3, parag. 1). Science News Report states that while there have been reports of convincing gene transfer and expression, there is little evidence of a therapeutic result in patients or animal models (Science 269, page 1050, col. 2, parag. 1, lines 6-15). Anderson states that in situ therapy, as contemplated in the specification by the direct administration of the gene to synovial cells, is hampered by effect ways for implanting corrected genes into various organs, as the genes are not expressed sufficiently to produce sufficient quantities of protein (Anderson (September 1995) Scientific American, 124-126 and 128). Blau states that expression and delivery are seen as the hurdles yet to be overcome for successful gene therapy (Blau (Nov. 2, 1995) The New England J. Med., page 1204, col. 1-2 bridg. Sent. and page 1205, col. 1-2 bridg. Sent.). Thus, for the general concept of gene therapy, with claim 1 as an example, the art at the time of filing taught that gene therapy was unpredictable.

In addition, the art at the time of filing teaches with regards to HSV-1 vectors, a neurotropic virus, teaches that the use of HSV-1 vectors in gene therapy protocols was unpredictable. In experiments with first generation HSV vectors, such as those specifically taught in the present specification, gene transfer and transient expression were readily obtainable, but that expression of the DNA sequence of interest was not for a sufficient length of time for effective treatment of neurodegenerative diseases (Fink, page 284,

abstract). Further, HSV vectors applied to gene therapy protocols exhibited a residual toxicity resulting from non-replicating vectors and silencing DNA sequence expression from persisting latent HSV genomes in neurons (Fink, page 284, abstract). In rats and mice infected with HSV mutants with reduced cytotoxicity, reporter gene expression was shown to transiently peak 2 days after infection and then becoming undetectable one-week post-inoculation (Fink, page 288, col. 3, lines 2-8). Others acknowledged the potential use of HSV as gene therapy vectors, but state that the wide spread use of HSV will be restricted until problems concerning the spread of the vector are solved and cytotoxic functions of the virus removed from the vector (Blomer, page 1398, col. 1, parag. 1, line 10 to col. 2, line 4). Eck further states with regards to HSV that the advantages of the vector are countered by difficulty in rendering a viral preparation totally free of replication-competent virus and the eliciting of a potent immune response that are toxic to the infected cell (Eck, page 89, col. 1, parag. 1, lines 9-13). Additionally, it logically follows that if the initial administration of an HSV vector causes a host immune response, subsequent administrations of the virus will be less effective because of a second immune response. Thus for these reasons the present, the art at the time of filing found gene therapy using an HSV vector or an HSV vector regulating expression form a LAT promoter to be unpredictable.

Guidance and Working Examples

As the art fails to supply the necessary teachings, it is incumbent on the specification to do so. While the specification need not disclose that which is know in the art at the time of filing, the corollary, the specification need to discloses that which is not known in the art at the time of filing, applies. While the skill level in gene therapy is considered to be high, the skilled artisan would need guidance on treatment protocols to achieve a therapeutic result from the method of delivery.

The guidance provided in the specification is not seen as sufficient to enable a gene therapy method using the vectors claimed. Applicant has not shown that the claimed method can deliver and express a gene sufficiently to cause the amelioration of symptoms associated with a disease. Applicant has not provided guidance as to which promoters would regulate expression sufficiently to achieve a therapeutic effect. The achieving of such expression levels is necessary requirement for gene therapy. Examples 4 and 5 (specification, pages 25-26) teach that the administration, by corneal abrasion, of an HSV vector comprising the DNA sequence for β- glucuronidase operatively linked to the HSV LAT promoter to adult MPS VII mice results in the detection of β-glucuronidase in brain and trigeminal ganglia (a facial nerve) of the mice. However, the mice, which are models for mucopolysaccharidosis VII due to mutations in their GUSB gene, are not described as showing any alleviation of symptoms associated with the disorder due to the treatment. The specification states that the expression of the GUSB gene for 4 months in brain and trigeminal ganglia re presents increases the therapeutic presence of ameliorative enzymes for a lysosomal storage disease (specification, page 26, lines 2-6). However, there is no evidence that the level of expression achieved, which was not specifically stated, correlates to a treatment for mucopolysaccharidosis VII or any other CNS associated disorder. The specification provides no guidance as to routes of delivery, promoters or neurotropic viral vectors to enable a therapy.

With specific regards to an HSV-1 vector expressing β-glucuronidase from the LAP1 promoter, a form of the LAT promoter, the number of cells expressing the enzyme decreased over time (Fink, page 288, col. 3, lines 6-14). Also, when a HSV-1 construct comprising a cDNA encoding β-glucuronidase operably linked to a LAT promoter was administered to MPS VII mice via corneal abrasion, glucuronidase positive staining cells were identified (Wolfe, page 381, col. 2, parag. 2). However, in these experiments,

quantative measurements of β-glucuronidase enzymatic activity could not be made because there was too little enzyme for the analysis (Wolfe, page 383, col. 1, parag. 1, lines 7-12). Reference is made that the HSV-1 vector regulating expression from a LAT promoter demonstrates the feasibility of using the vector in gene therapy protocols, but it is also stated that "too few cells have been corrected at this stage to alter the disease phenotype" (Wolfe, page 383, col. 2, lines 1-7). Thus for these reasons the present, the art at the time of filing found gene therapy using an HSV vector or an HSV vector regulating expression form a LAT promoter to be unpredictable.

Therefore, as the specification provides no guidance over than that provided by the art, and the art's clear comments that gene therapy using any vector system, an HSV vector or an HSV vector regulating expression of a DNA sequence of interest was enabled at the time of filing, to implement the presently claimed invention would require the skilled artisan to engage in an undue amount of experimentation without a predictable degree of success.

(11) Response to Argument

Appellant argues that the disclosures meet the requirements for enablement as set forth in MPEP 2164, to make and use the claimed invention at the time of filing (Brief, page 10, lines 8-13). Appellant argues that the claims are to methods for delivery of selected DNA sequences to the central nervous system (CNS) of a mammal comprising administering to peripheral neuron cells of a mammal a neurotropic viral vector that infects the CNS of a mammal so that the selected DNA sequences are stably expressed for at least four months by the CNS cells (Brief, page 10, lines 13-19). Appellant argues the selected DNA sequence is operably linked to a LAT promoter to facilitate stable expression (Brief, page 10, lines 19-21). Appellant argues that the claims are not to methods of treating a disease of the CNS, but to stably expressing a selected DNA sequence in the CNS (Brief, page 10, lines 21-25).

Appellant argues that each element of the claimed invention is disclosed: how to administer to the peripheral neuron cells (page18, lines 3 to page 19, line 20, and pages 19 and 20, bridg. parag.), a neurotropic viral vector that infects cells of the CNS (pages 10 to 11, bridg. parag. and page 15, lines 3-31) containing a selected DNA sequence (pages 9 to10, bridg. parag. and page 16, parag. 1) operatively linked to a LAT promoter (page 13, line 8 to page 9, line 35) so that said selected DNA sequence is stably expressed for at least four months by infected CNS (Brief, page 10, line 25 to page 11, line 5). Appellant argues the specification teaches at least one use for the method of stably expressing, to correct a deficiency in a biological function in cells of the CNS (Brief, page 11, lines 5-8). These arguments are not persuasive.

The enablement rejection subject to this Appeal is that the claims lack an enabled use. A review of the disclosure reveals that appellant at the time of filing only disclosed the claimed method of stable expression for methods of treatment. No other uses for the method are disclosed. Thus, the skilled artisan reading the claims in light of the specification would determine that the intended use of the methods claimed is for methods of treatment. Although the claims, as written, are to methods of stable expression, the use of the claims is for methods of treatment. The claims must have an enabled use. At no place in the specification, and no such place as been shown by Appellant, is there guidance to a use of the methods other than a therapeutic use. The specification is very clear that the use for the method of stable expression is for a therapeutic effect, that the methods are disclosed as gene therapy methods for CNS disorders (specification, page 2, line 3 to page 3, line 17; page 8, lines 9-13; page 9, line 34 to page 10, line 9; page 16, lines 1-17 and page 20, lines 7-10). The teachings of the specification regarding neurotropic vector, selected DNA sequences, the LAT promoter, modes of delivery, and stable expression can only be regarded as part of a gene therapy. The rejection is that the only use of the method, when

read in light of the specification, as a gene therapy for CNS disorders, is not enabled. What are the use of the method claimed if not a therapeutic use? The specification provides no guidance towards a use absent a therapeutic one. Additionally, appellant has failed to point to another disclosed use.

Appellant argues that a demonstration of therapeutic benefit is not a requirement for patentability (Brief, page 12, lines 2-3). Appellant argues that the case law is clear that applicants do not have to prove correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty (Brief, page 12, lines 4-6). Appellant argues that for patentability there does not have to be evidence of success in treating humans where such a utility is asserted (Brief, page 12, lines 7-8). Appellant cites MPEP 2164.02 as stating that because something has not been done previously is not sufficient basis for rejection in all applications purporting to disclose how to do it (Brief, page 12, lines 8-13). Appellant argues that the Examiner's requirement that the specification demonstrate a therapeutic effect or benefit to the host is improper (Brief, page 12, lines 14-15). Appellant argues that the courts, citing *Nelson v Bowler*, 626 F.2d 853, 206 USPQ 881, 884, CCPA 1980, have held that all that needs to be shown is a reasonable correlation between the activity and the asserted use (Brief, page 12, lines 16-19). Appellant argues of one of skill in the art would accept the data provided as being reasonably predictive of utility in human, evidence from these tests should be considered sufficient to support the credibility of the assert utility (citing *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Krimmel*, F.2d USPQ 215, 219 (CCPA 1961); *Ex parte Krepelka*, 231 USPQ 746 (Bd. Pat. App. & Inter. 1986) (Brief, page 12, lines 19-25). Appellants argue that a declaration by Dr. Laura Plunkett, which stated the data provided in the instant specification are demonstrative of a pharmacological effect, delivery of a gene to the CNS of an animal and expression of that gene, and thus, therapeutic utility (Brief, page

12, line 25 to page 13, line 1). Appellant refers to paragraphs 3 and 4 of Dr. Plunkett's declaration (Brief, page 13, lines 2-3). Appellant argues that the teachings of the specification in conjunction with general knowledge in the art establishing strategies for use of this delivery system in human as well as for the production of animal models as evidenced by Xing et al (1994) (Brief, page 13, lines 6-10). Appellant argues that confirmation of this approach can be found in medical pharmacology and have submitted a chapter of *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 1996, devoted to gene therapy (Brief, page 13, lines 11-15). Appellant argues pharmacologists view gene therapy as another tool for drug delivery that has reached acceptance as one of many tools in pharmacology (Brief, page 13, lines 16-18). These arguments are not persuasive.

> The arguments presented by appellant are directed to a rejection under 35 U.S.C. § 101 as lacking a credible utility. However, the rejection of record is not under this statute but under 35 U.S.C. § 112, first paragraph, how to use. Thus, appellant's arguments are moot, as they do not address whether or not the specification teaches the skilled artisan at the time of filing how to use the claimed invention. There has been not request on this record for evidence of statistical certainty not for human data. With regard to the Plunkett declaration, paragraphs 3 and 4, there is no discussion that the claims would have an enabled use given the disclosure of the specification. Whether it is called "therapeutic benefit" or enablement, a method of gene therapy must be enabled so that there is a prediction of success without undue experimentation. Declarant Plunkett's statements are that the invention has utility, not that it is enabled. Further, Declarant Plunkett discusses the FDA and the drug approval process. This is not the issue here. The FDA and the PTO have different standards and different objectives. At no point does Declarant Plunkett discuss that the claimed invention would predictably be expected to alleviate a symptom of any disease in any animal model using the claimed methods.

Xing discloses a rat model where an IL-6 transgene was administered to lung epithelium of rats by the intratracheal delivery of a human adenovirus comprising a DNA sequence encoding IL-6. Xing states that their model is for investigating cytokine function in vivo. The relevance of this references to the present Appeal is not clear. Xing does not deliver DNA sequences encoding cytokines or any other protein to the CNS using a neurotropic virus via the peripheral nervous system. The methods of Xing are materially different and separate from those claimed. Xing does not support for the enablement of the claimed invention because there are no relevant teachings in Xing.

Goodman & Gilman support the general lack of enablement of gene therapy in stating that "the clinical application of gene therapy is more limited by the availability of suitable gene transfer methodology than by the identification of suitable targets for gene alterations" (Appendix C, page 99, col. 2, parag. 1, lines 11-15). Further, it is noted that Goodman & Gilman do not disclose any successful gene therapy protocols. While pages 79-81 discloses phase I trials, these trials are for safety and are not evidence of enablement for any gene therapy protocol. Further, the rejection of record contains evidence from several skilled artisans that gene therapy in general at the time of filing was not enabled (see rejection above, in particular Verma et al, Science News Reports, Anderson, and Blau). The rejection further contains evidence that gene therapy for particular disease disclosed in the specification was not enabled at the time of filing (see rejection above Blomer et al, Fink et al and Wolfe et al). The enablement rejection was not made of opinion but made from a review of the art as a whole at the time of filing, and supporting evidence post filing.

Appellant argues that the examiner suggests that neurotropic viruses have not been shown to have a therapeutic effect in a host. Appellant argues that this is improper because a therapeutic demonstration is improper. Appellant argues that working examples of every embodiment of the claim are not required. Appellant argues that the propriety of such a rejection involves a two-stage inquiry, where the first stage determines how broad the claim is and the second stage is to determine if on of skill in the art can make and use the entire scope of the claim without undue experimentation. Applicant argues that the specification discloses other neurotropic viruses, and that US Patent 5,849,572 teaches that an HSV virus provides expression for up to 6 months post-inoculation. These arguments are not persuasive.

The only place in the rejection where question is raised regarding other neurotropic viruses is in the context of enablement for gene therapy. The rejection is that post filing art

using the same HSV vector comprising a DNA sequence encoding a glucuronidase operably linked to a LAT promoter taught that this vector was not effective in a gene therapy protocol administered to a mouse model of mucopolysaccharidosis VII (see rejection, above). If HSV is not enabled then, other neurotropic viruses likewise would lack enablement given this teaching and those of Verma, Science News Report, Anderson, Blau, Fink, Blomer, and Wolfe cited above. This is a reasonable rejection to make. Again, the claims, when read in light of the specification, are to methods of gene therapy. The rejection makes appellants two-stage inquiry. US Patent 5,849,572 contains claims to an HSV vector comprising a LAT promoter operably linked to a DNA sequence of interest. There are no method claims. The specification discloses six months expression of a marker protein when the HSV vector in injected into the brain. This does not support the enablement of the claimed invention, as there is no therapeutic effect obtained by the injection of the vector into the brain. In fact, a disease model was not the subject of the HSV vector injection.

Respectfully submitted,
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April 4, 2005

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